

REVIEW

by Prof. Elena Nikolova Piperkova, MD, DSC

Head of the Clinic of Nuclear Medicine

Specialized University Hospital for Active Treatment in Oncology – Sofia

of the dissertation thesis awarding the educational and scientific degree

“Philosophy Doctor”

in the field of higher education 7. Health and sports,

professional field 7.1. Medicine,

Scientific speciality " Medical radiology, and X-ray treatment (including use of radioactive isotopes)" coded 03.01.28.

Marina Ivanova Dyankova, MD

Department of Imaging Diagnostics, Interventional Radiology and Radiotherapy

Faculty of Medicine

Medical University “Prof. Dr. Paraskev Stoyanov” - Varna

Thesis subject:

68Ga-PSMA PET/CT IMAGING IN PROSTATIC CARCINOMA.

ADVANTAGES AND POSSIBLE DIAGNOSTIC ERRORS

Distinguished members of the Academic Advancement Board,

By Order № P-109-199/29.04.2022 of the Rector of MU-Varna and as a member of the AAB, I was appointed to participate with a review of the doctoral thesis of Dr. Marina Ivanova Dyankova for the defence of her PhD degree.

1. Significance of the problem and formulation of the aim and tasks

Prostate cancer (PC) shows a statistically high increase in morbidity in the last decade worldwide, including in our country, and ranks first among malignant diseases in men. PC is of a complex heterogeneous nature, with the presence of hormone-dependent and hormone-resistant populations, including the possibility of solid dedifferentiation and the presence of somatostatin receptors. Early diagnosis, accurate staging and re-staging of a clinically non-manifested bone metastatic process, and the detection of biochemical recurrence are critical to the individualised therapeutic approach, risk stratification, and improving the patient's prognosis and quality of life. Research in refining and improving the diagnostic accuracy in PC is a crucial current issue aimed at improving survival and the quality of life of prostate cancer patients. The present thesis focuses on the latest high-tech

hybrid method – ^{68}Ga -PSMA PET/CT, demonstrating its advantages over other imaging methods. The details of the proper conduct of the study must be specified to reduce false positive (FP) and false negative (FN) results, defining the rules to avoid possible artefacts in the study and diagnostic errors in interpreting results.

The aim of the thesis evolves from an extensive study reflected in a detailed and, at the same time, concise and meticulous literature review. The aim is clearly formulated, and the candidate correctly sets the six tasks to achieve it. The tasks are formulated clearly and properly and correspond to the aim of the research.

2. Structure of the thesis

The thesis is structured clearly and precisely, meeting the requirements. It contains 197 pages, 3 appendices, 85 figures and 50 tables. It is systematised in the following chapters: Introduction, literature review, aim and tasks, materials and methods, results and discussion, conclusions, contributions and recommendations. It is preceded by a list of abbreviations for better comprehension and clarity of the text. The proportions between the individual sections are observed. Each section of the dissertation follows the logic of the tasks set for achieving the aim, and the conclusions unfold naturally from the results, statistical data processing and discussions.

3. Literary awareness of the candidate

The bibliography is sufficiently in-depth and up-to-date, including 212 cited literature sources, of which 11 are in Cyrillic and 201 in Latin, the majority of them published after 2014, without neglecting the published previous experience.

The literature review of the thesis is 36 pages, with a comprehensive analysis of the current application ^{68}Ga -PSMA PET/CT. It demonstrates the lack of generalised and systematised data on the application of the method on PC. It shows that there is still no algorithm for diagnostic methods and no personalised approach in the strategy of applying various diagnostic methods in the different stages of monitoring the disease considering the treatment effect. The conclusions from the literature review are specific and justify the aim and tasks of the research.

4. Methodological level and research design

The study included 386 patients for a period of two years – 2019-2021, in which staging and restaging ^{68}Ga -PSMA PET/CT tests were performed. The study covers patients who are distributed precisely into separate groups according to developed strict criteria related to the set tasks, which allows drawing the corresponding conclusions. The results are processed using adequate statistical methods.

The research methods chosen by the author and the clinical material allow to achieve the aim, and the set tasks have received relevant results.

5. Correspondence between the aim, the results and the conclusions

There is a logical correspondence between the set aim, the obtained results, the discussion and the conclusions. The author's research results and discussion are set out on 118 pages and are richly

illustrated. The patients' groups tag along the course of the set tasks and are presented in detail. The significance, advantages and possible diagnostic errors of the ^{68}Ga -PSMA PET/CT method are indicated, including the possible variations in physiological PSMA-activity, the pathological expression of PSMA antigen unrelated to CP, as well as the false negative findings,

The presented data from the applied diagnostic algorithm for PC staging show a thorough and detailed analysis of the different patients' groups according to the stage and PSA values and an in-depth analysis of the possible diagnostic limitations and errors, which stipulates high reliability of conclusions.

^{68}Ga -PSMA PET/CT was used in a large cohort of patients with biochemical recurrence of prostate cancer after radical therapy (n = 133). The prognostic factors for the positivity of PSMA-PET results, the factors related to the detection rate, as well as the advantages of the method over CT scans have been determined. The application of the PSMA PET/CT method in patients with biochemical progression after radical prostatectomy (n = 144) in a wide range of tumour marker values (with an emphasis on low PSA levels, including < 0.2 ng/mL) was investigated. The effect of PSA values on sensitivity and PSMA-PET detection rate was determined. The use of PSMA-PET in the initial regional nodal (N) and distant metastatic (M) staging of patients with intermediate and high-risk primary prostate cancer (n = 109) was thoroughly analysed. The advantages of PSMA-PET over conventional CT scans were determined, and possible diagnostic errors have been investigated. The efficacy of ^{68}Ga -PSMA PET/CT on (N, M) staging of patients with primary prostate cancer according to risk before radical therapy (n = 69) and in comparison with the conducted conventional imaging methods (CT, MRI and bone scintigraphy) was determined. The application of the method in patients with ISUP grade 5 (n = 61) was established. The features of nodal and bone metastasis and the correlation between the detection rate for different localisations of malignant involvement of prostate cancer and PSA values and clinical T stage were analysed. ^{68}Ga -PSMA PET/CT was used for the analysis of anatomical models of metastatic involvement of recurrent and primary PC (in 386 patients). The correlations between pathological PSMA PET/CT image results and serum PSA values, Gleason score/ISUP grade, clinical T stage and other factors in primary PC (n = 109), after radical therapy (n = 133), and in biochemical progression after radical prostatectomy (n = 144) were investigated. The calculated parameters of the hybrid method were thoroughly evaluated in terms of: detection rate, sensitivity, specificity, PPV, NPV and accuracy, including the risk of false positive and false negative results in the studied groups of patients.

6. Analysis of the conclusions and contributions

The thesis is completed with 10 conclusions and 10 contributions formulated in detail and clarity. The conclusions can be combined and reduced in number, but they are also highly informative and give weight to each result obtained. The contributions are of great importance as this is the first study on the diagnostic possibilities of ^{68}Ga -PSMA PET/CT in prostate cancer in Bulgaria on such a large, in-depth scale and analysis. For the first time in Bulgaria, recommendations have been made for the practical application of this high-tech hybrid imaging method. The recommendations are based on the study of a large number of PC patients, including patients with biochemical progression after radical prostatectomy, with the initial staging of high-risk groups and evaluating

the diagnostic capabilities of ^{68}Ga -PSMA PET/CT in primary staging of patients with low PSA values or with ISUP grade 5.

7. Critical remarks and recommendations

I have no critical remarks questioning the methods, the presented evidence, the discussion of the results obtained and the conclusions drawn.

8. Publications and scientific events

The results of the candidate's research on the thesis subject are published in 1 scientific journal and the papers of 2 scientific forums. One of the papers is of great scientific value and, after review, was published in the European Journal of Nuclear Medicine and Molecular Imaging (Eur JNM 2020) with an impact factor.

9. Personal impressions of the candidate

Dr. Marina Ivanova Dyankova is an established specialist in Nuclear Medicine. I have immediate impressions of the practical and theoretical training in Nuclear Medicine. She is responsible and thorough in her work and clinical and scientific research. She is interested not only in her daily work but follows the innovations in our field, eager to implement innovative diagnostics for the benefit of patients quickly. The candidate treats managers, colleagues and patients with respect. She is accurate, precise and ethical and has qualities for teamwork and continuous improvement.

10. Conclusion

Based on the scientific merits of Dr. Marina Ivanova Dyankova's thesis, the relevance of the subject and established results, significant conclusions and contributions of the candidate, I strongly recommend to the members of the distinguished Academic Advancement Board to award the educational and scientific degree "PHILOSOPHY DOCTOR" to Dr. Marina Ivanova Dyankova for her thesis " ^{68}Ga -PSMA PET/CT IMAGING IN PROSTATIC CARCINOMA. ADVANTAGES AND POSSIBLE DIAGNOSTIC ERRORS "



April 16, 2022

Sofia

Prof. Elena Piperkova, MD, DSC